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16. ABSTRACT

A committee of scientists was established by the U.S. Environmental Protection Agency to appraise the current state of aneuploidy test methodology, to compile and analyze published data on the chemical induction of aneuploidy, and to provide guidance for additional test development and validation. The committee was organized into 9 working groups, representing different eukaryotic organisms ranging from fungi to whole mammals. The Environmental Mutagen, Carcinogen, and Teratogen Information Program at Oak Ridge National Laboratory identified and provided literature to the working groups. The 9 reports were prepared by the individual working groups. The reports include: (1) descriptions of the available testing approaches and general principles to be followed for protocol development, (2) criteria for evaluating data, and (3) recommendations for future test development and basic research. The evaluated results are presented in tables. For the positive and negative calls, the lowest effective dose tested or the highest ineffective dose tested, respectively, and the range of concentrations tested are provided. An overall summary report was prepared that summarizes the conclusions and recommendations of the 9 working groups and the chemical data base. It is hoped that these reports will provide a framework for further test development and validation of aneuploidy assays.

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An introduction to a series of U.S. Environmental Protection Agency special committee reports on testing approaches for the detection of chemically induced aneuploidy *

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Summary

A committee of scientists was established by the U.S. Environmental Protection Agency * to appraise the current state of aneuploidy test methodology, to compile and analyze published data on the chemical induction of aneuploidy, and to provide guidance for additional test development and validation. The reports that follow in this special issue of Mutation Research, document the urgent need for test method development and validation in this important area of environmental mutagenesis, and provide directions for further research.

There are a myriad of human diseases that are caused by or associated with gene or chromosome mutations (McKusick, 1979). Many chemicals that are released into the environment have been shown to induce these genetic alterations in experimental organisms, and thus much effort has been directed to the development and validation of bioassays for the detection of such agents. Although many assays exist for detecting chemically induced gene mutations or chromosome breakage, specific tests for the detection of aneuploidy (loss or gain of whole chromosomes) are necessary because the underlying mechanisms of its induction are likely to be different from those types of genetic damage that involve DNA as the principal target.

Aneuploidy tests are important in evaluating genetic hazards because aneuploidy is common in humans and known to have a serious impact on human health (Hook, 1983, 1985; Bond and Chandley, 1983). The frequency of aneuploidy in newborns is no less than 0.3% (Hook and Hamerton, 1977). Disorders resulting from aneuploidy exhibit physical, intellectual, and behavioral abnormalities (e.g., Down syndrome, Edward syn-

* The views expressed in this paper are those of the authors and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency.

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* This committee was directed by the Reproductive Effects Assessment Group and the Health Effects Research Laboratory within the Office of Research and Development, U.S. Environmental Protection Agency.

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drome, Patau syndrome, Klinefelter syndrome, and Turner syndrome). Because it produces a gene imbalance, aneuploidy is likely to be lethal: approximately 33% of early fetal wastage and 5–7% of infant deaths are attributable to meiotic chromosome malsegregation (Hook, 1983). Aneuploidy can also arise in somatic cells. Mitotic aneuploidy occurring soon after fertilization could result in fetal wastage or in offspring that exhibit phenotypes of aneuploid genetic diseases. Finally, there is evidence that mitotic aneuploidy may play a role in the development of some cancers (Kondo et al., 1984; Tsutsui et al., 1983; Cavenee et al., 1983; Evans, 1985; Barrett et al., 1985). It remains controversial whether exposure to chemical (or physical) agents has ever increased the incidence of aneuploidy in the human population (Kline and Stein, 1985). Although some studies do suggest this possibility (Kline et al., 1980; Strobino et al., 1980; Rapaport, 1956; Uchida, 1977; Alberman et al., 1972), there may be confounding factors or other explanations for these results. Nonetheless, because of the high frequency and the clinical impact of human aneuploidy, efforts to identify potential aneuploidy-inducing chemicals appear warranted.

TABLE 1

THE ANEUPLOIDY DATA REVIEW COMMITTEE

Organization	Committee members
Coordinators	Dr. Vicki L. Dellarco (U.S. EPA)
	Dr. Jan C. Liang (Univ. Texas)
	Dr. Michael D. Waters (U.S. EPA)
EMCT	Dr. Kathleen H. Mavournin (ORNL)
Working groups	
Saccharomyces	Dr. Vernon W. Mayer (FDA)
	Dr. Michael A. Resnick (NIEHS)
	Dr. F.K. Zimmermann (Technische Hochschule, F.R.G.)
Aspergillus	Dr. Etta Käfer (McGill Univ., Canada)
	Dr. Andreas Kappas (Nuclear Research Center, Greece)
	Dr. Barry R. Scott (Phoenix Lone Oak Labs, Texas)
Neurospora	Dr. Herman E. Brockman (Illinois State Univ.)
	Dr. David M. DeMarini (U.S. EPA)
	Dr. Fredrick J. de Serres (NIEHS)
	Dr. A.J.F. Griffiths (Univ. British Columbia)
Higher plants	Dr. Milton J. Constantin (Univ. Tennessee)
	Dr. Shabeg Sandhu (U.S. EPA)
	Dr. Baldev K. Vig (Univ. Nevada)
Drosophila	Dr. James M. Mason (NIEHS)
	Dr. Chris Osgood (Univ. Kentucky)
	Dr. Stanley Zimmering (Brown Univ., Rhode Island)
Mammalian cells in culture	Dr. James L. Ivett (Litton Bionetics, MD)
	Dr. Sheila M. Galloway (Merck, Sharpe, Dohme, Pennsylvania)
Mammalian somatic cells in vivo	Dr. Michael C. Cimino (U.S. EPA)
	Dr. Jan C. Liang (Univ. Texas)
	Dr. Raymond R. Tice (Brookhaven Natl. Lab.)
Mammalian male germ cells in vivo	Dr. James W. Allen (U.S. EPA)
	Dr. Anthony V. Carrano (Lawrence Livermore Natl. Lab.)
	Dr. Jan C. Liang (Univ. Texas)
	Dr. R. Julian Preston (ORNL)
Mammalian female germ cells in vivo	Dr. K.S. Lavappa (FDA)
	Dr. John B. Mailhes (Louisiana State Univ.)
	Dr. R. Julian Preston (ORNL)

Aneuploidy Data Review Committee

7 years ago, the U.S. EPA initiated the Gene-Tox Program to evaluate the status of bioassays used in genetic toxicology (Waters, 1979; Waters and Auletta, 1981). Aneuploidy data were evaluated by the Gene-Tox working groups on Drosophila and on fungal systems, but tests for the induction of aneuploidy in mammalian and plant systems were not reviewed. In 1984, an expert committee was established by the U.S. EPA to review the current status of test methodologies for aneuploidy induction. This review effort could not be based on standarized protocols since, presently, these do not exist. Evaluation of the various test systems was accomplished through a critical review of the available literature on the chemical induction of aneuploidy.

Organization

The committee was organized into 9 working groups, representing different eukaryotic organisms ranging from fungi to whole mammals (Table 1). Certain test systems (e.g., Sordaria, Melanoplus) were not included in this review because there was insufficient information to appraise their performance; in the future these test organisms should be investigated more fully. Each working group consisted of 2–4 scientists. The Environmental Mutagen, Carcinogen, and Teratogen Information Program (EMCT) at Oak Ridge National Laboratory (ORNL) identified and provided literature to the working groups. EMCT assisted in the design of data entry forms to record evaluations of published data, and in computerization and analysis of the extracted data.

Literature search and selection

The Aneuploidy File produced by EMCT was the principal resource for identifying papers to be reviewed; this bibliographic data base covers the literature on aneuploidy from 1970 to the present. Because considerable data on Drosophila and plant systems were published before 1970, a systematic search of the Environmental Mutagen Information file at EMCT and the TOXLINE files of the National Library of Medicine was done to locate earlier papers on these organisms. Evaluations were limited to papers providing detailed primary data; review articles and abstracts were not included. Some information not published in journal form (e.g., grant reports) was accepted if it was available to the public through EMCT or the National Technical Information Service (Springfield, VA); these sources are identified in the reports on individual assay systems. In general, only papers in English or in English translation were used.

The entire review was restricted to aneuploidy induction by defined chemical agents; physical agents, complex mixtures, or combinations of agents were not considered. Definitive work on radiation effects or experimental conditions (e.g., pH, temperature) was included in discussions on the historical development of certain test protocols.

Evaluation criteria

The evaluation process followed by the working groups is depicted in Fig. 1. Initially, the working groups screened the papers provided by the EMCT: papers were rejected and not further evaluated for the following reasons: (i) lack of relevant data or

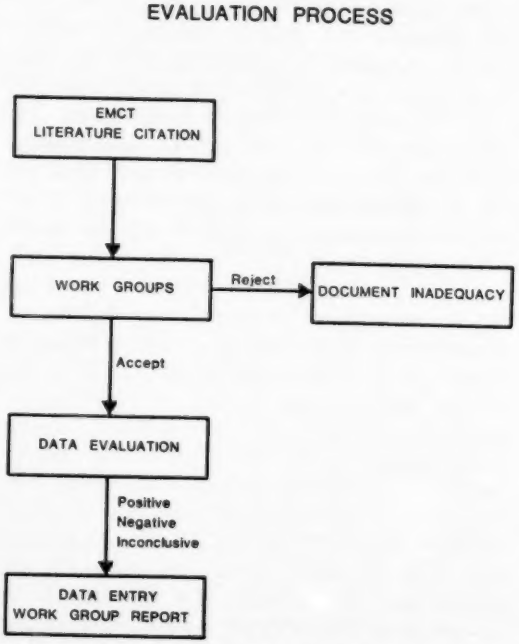

Fig. 1. The Aneuploidy Data Review Committee evaluation process.

insufficient data to make an independent evaluation of results, (ii) lack of appropriate control data, or (iii) insufficient description of experimental protocols or improper experimental protocols. Individual working groups defined relevance and applied additional criteria specific for their test system. Reasons for rejection of specific papers are documented at the EMCT.

After the initial screening, the experimental results in the remaining papers were further classified as positive, negative, or inconclusive. Data entry forms developed by the committee were used to record the working groups' evaluations of the classified papers. The criteria imposed for these evaluations are listed in the individual working group reports. Because definitive protocols have not been established for aneuploidy assays, it is difficult at this stage to apply precise criteria for evaluating results. As this area of testing develops, it is likely that new criteria will by introduced.

Presentation of analysis

The reports that follow were prepared by the individual working groups and edited at EMCT with assistance from Eleanor T. Rogers, Information Research and Analysis Publications Office, ORNL. The reports include: (i) descriptions of the available testing approaches and general principles to be followed for protocol development, (ii) criteria for evaluating data, and (iii) recommendations for future test development and basic research. The evaluated results are presented in tables. For the positive and negative calls, the lowest effective dose tested (LEDT) or the highest ineffective dose tested (HIDT), respectively, and the range of concentrations tested are provided. The definitions of LEDT and HIDT can be found in Garrett et al. (1984). Briefly, the LEDT is the minimal effective concentration for a positive response. For a negative test, the HIDT is the highest concentration tested without producing extreme toxicity. If a single concentration was tested, this concentration was considered equivalent to LEDT or HIDT. The LEDT and HIDT values were used to evaluate the activity of selected chemicals, the performance of particular test systems, or to analyze data comparatively across different test systems.

It is hoped that these reports will provide a framework for further development and validation of aneuploidy assays.

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